REMARKS

In the Office Action dated July 23, 2003, claims 1-37 are pending. Claims 1-15, 25-27 and 29 are under examination insofar as these claims read on the elected species of noggin as a BMP antagonist. Claims 16-24, 28 and 30-37 are withdrawn from further consideration as drawn to nonelected subject matter. Claim 29 is objected to allegedly because claim 29 is dependent on claim 28, which is withdrawn from consideration. Claim 25 is objected to under 37 C.F.R. §1.75 as a substantial duplicate of claim 3. Claims 3-9 and 25-27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly unpatentable over claims 13-15 and 20 of co-pending application Serial No. 09/670,198. Claims 4-12 and 25-27 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Claims 1, 2, 13-15 and 29 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Thomson (US Patent 5,843,780). Claims 1, 2, 3, 13-15 and 29 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Carpenter et al. (Pub. No. US2002/0019046 A1). The Examiner has acknowledged that claims 4-12 and 25-27 are free of the art of record. The Examiner has also requested copies of the priority documents. In addition, the Examiner has objected to the abstract of the application because it is not presented as a single paragraph.

This Response addresses each of the Examiner's rejections and objections. Applicant therefore respectfully submits that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

In the Office Action, the Examiner has acknowledged the applicant's priority claim based on applications PR1327 and PQ8242, filed in Australia on November 8, 2000 and June 20, 2000, respectively. The Examiner points out that the applicant has not filed certified copies of

these Australian applications. Applicants provide herewith certified copies of the Australian priority applications. Applicants' priority claim is therefore perfected.

The Examiner has also objected to the abstract of the application, because the abstract was not presented as a single paragraph. Applicants have amended the abstract as a single paragraph. The new abstract is also provided on a separate page. The objection to the abstract is therefore overcome. Withdrawal thereof is respectfully requested.

Claim 29 is objected to allegedly because claim 29 is dependent on claim 28, which is withdrawn from consideration. Applicants have amended claim 29 to delete the reference to claim 28. As such, the objection to claim 29 is overcome and withdrawal thereof is respectfully requested.

Claim 25 is objected to under 37 C.F.R. §1.75 as a substantial duplicate of claim 3. Applicants have canceled claim 3 and dependent claim 13 without prejudice. The objection to claim 25 is therefore overcome and withdrawal thereof is respectfully requested.

Claims 3-9 and 25-27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly unpatentable over claims 13-15 and 20 of co-pending application Serial No. 09/670,198.

It is observed that the present application has been assigned to ES Cell International. It is believed that the '198 application has been assigned to a different party, although there appears to be at least one common inventor named in the '198 application and the present application. It is further observed that the rejection is provisional and the '198 application has not issued. Therefore, Applicants respectfully request withdrawal of the rejection.

Claims 4-12 and 25-27 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

In the first instance, the Examiner questions whether the instantly claimed method, which employs noggin (a BMP antagonist), can be used to culture ES cells other than those obtained from humans. The Examiner acknowledges that the present specification demonstrates that human ES cells, cultured in the presence noggin, gave rise to an undifferentiated cell type lacking stem cell markers. However, the Examiner argues that, as known in the art, ES cells differ from species to species; and in particular, human ES cells differ in their *in vitro* culture requirements as compared to ES cells from mouse, rat or hamsters. Therefore, the Examiner reasons that, given the evidence of record, what is observed with human ES cells will not necessarily extend to any other ES cells obtained from other species.

In order to delineate a preferred embodiment of the present invention, Applicants have added new claim 45, which depend upon claims 4 and 25, and recite that the undifferentiated ES cells are of human origin. Support for claim 45 is found in the specification, e.g., at page 7, lines 25-27 and Figure 7; page 8, lines 1-9, and Figures 8-10; and page 29, lines 13-27.

Applicants further submit that the claimed methods are generally applicable to ES cells of other origins, not just human ES cells. As supporting evidence, Applicants provide herewith an article by Theresa E. Gratsch and K. Sue O'Shea, entitled "Noggin and Chordin Have Distinct Activities in Promoting Lineage Commitment of Mouse Embryonic Stem (ES) Cells" *Developmental Biology* 245, 83-94 (2002) (attached hereto as **Exhibit 1**). The authors used essentially the same techniques as described in the present application and demonstrated that noggin also caused the neuronal differentiation of mouse embryonic stem cells.

Furthermore, the Examiner questions the nature of the resulting cells after practicing the method steps of culturing ES cells with an antagonist of a BMP pathway, in particular,

culturing the ES cells with the elected species of noggin. Presently, claims 4-12 are directed to a "method of producing a progenitor cell"; and claims 25-27 are directed to a "method of culturing an undifferentiated ES cells". Referring to page 29, lines 17-19, the Examiner alleges that, in light of the specification, treating human ES cells with noggin results in a cell that has not been fully characterized. The Examiner observes that the resulting cells are not neuronal progenitor cells, as these cells lack neuronal cell markers. The Examiner acknowledges, however, that the specification provides evidence that the noggin treated human ES cells are capable of differentiating into neuronal and glial cells. The Examiner admits that the noggin treated cell appears to be an intermediate cell type. However, the Examiner argues that there is no objective evidence that the resulting noggin treated cell is a progenitor cell capable of giving rise to any somatic lineage. According to the Examiner, the resulting cell can only be characterized as a cell lacking the original ES cell markers.

Applicants respectfully submit that treating ES cells with noggin indeed results in an intermediate cell type, as stated by the Examiner. This intermediate cell type, presently recited as "a progenitor cell", lacks original ES cell markers, and lacks neuronal cell markers. Yet, this "progenitor cell" can be cultured to produce neuronal progenitor cell, as admitted by the Examiner and as described in the specification at page 15, lines 16-26, and page 29, lines 13-16. To further characterize these features of the progenitor cell, Applicants have amended claim 4 to recite that "said progenitor cell lacks at least one marker of said undifferentiated ES cell" and have added claims 46-49. Support for claims 46-49 is found in the specification, e.g., page 15, lines 16-26; page 29, lines 13-16; and page 28, lines 15.

Applicants respectfully submit that the presently claimed subject matter is adequately taught in the specification in a manner that would enable those skilled in the art to practice the

claimed invention without undue experimentation. As such, the rejection under 35 U.S.C. §112, first paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 1, 2, 13-15 and 29 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Thomson (US Patent 5,843,780). It is observed that claims 1, 2 and 13 are drawn to undifferentiated ES cells. Claim 14 is drawn to a progenitor cell. Claims 15 and 29 are directed to an "undifferentiated ES cell or a progenitor cell".

The Examiner contends that Thomson teaches primate embryonic stem cells, which are pluripotent and capable of giving rise to the various somatic cell lineages. Furthermore, with respect to the claimed undifferentiated ES cells as a product by process (claims 13, 14, 29 and in part 15), the Examiner contends that the claimed cells are identical or substantially identical to those disclosed by Thomson. Specifically, the Examiner states that, although the undifferentiated ES cells or progenitor cells are produced by culturing ES cells in the presence of noggin, the claims do not set forth any particular effect of noggin on the cultured ES cells. Therefore, the Examiner states that the undifferentiated ES cells and progenitor cells, as presently claimed, are being interpreted to be cells capable of giving rise to any cell type of any lineage, and are therefore anticipated by Thomson.

Furthermore, with respect to the specific antibody markers recited in claim 15, the Examiner contends that these represent markers on ES cell cultures which are allowed to spontaneously differentiate. The Examiner reasons that, because the primate ES cells described by Thomson are highly pluripotent and not subject to differentiating culture conditions, the cells would not entail any of these cell surface markers and therefore anticipate the presently claimed "undifferentiated ES cells".

In response, Applicants have canceled claims 1-2 without prejudice. Applicants reserve the right to pursue the subject matter of claims 1-2 in a continuation application. Claim 13 is also canceled, as discussed above. Therefore, the rejection insofar as claims 1-2 and 13 is concerned, is rendered moot.

Claim 14, as presently amended, is drawn to a progenitor prepared by the method of any one of claims 4 or 46-48. As submitted above, claim 4 has been amended to further characterize the progenitor cell as lacking at least one marker of the undifferentiated ES cell, as a result of the culturing of the ES cell in the presence of noggin. Claims 46-48 delineate additional features the progenitor cell may entail, i.e., lacking at least marker of a neuronal progenitor cell, reactive to an antibody against the 68Kd neurofilament protein, and capable of differentiating into a neuronal cell, respectively. Thomson merely teaches pluripotent ES cells or cells spontaneously differentiated from pluripotent ES cells. It is respectfully submitted that Thomson does not teach a progenitor cell as characterized in any of claims 4 or 46-48. Therefore, the progenitor cell of claim 14 is not taught by Thomson.

Claim 15 has been amended to delete the references to canceled claims 1 and 13, as well as the recitation "undifferentiated ES cell", which is prepared by original claims 1 or 13. As discussed above, Thomson does not teach the progenitor cell of claim 14 as presently recited. Therefore, claim 15, which further characterizes the progenitor cell of claim 14, is not taught or suggested by Thomson either.

Claim 29, as amended, is drawn to an undifferentiated ES cell prepared by the method of claim 25 and characterized by a lack of at least one marker of the undifferentiated ES cells prior to the culturing. Thomson does not teach an undifferentiated ES cell produced by culturing undifferentiated ES cells in the presence of noggin and characterized by a lack of at least one

marker of the original undifferentiated ES cells prior to the culturing. Therefore, the undifferentiated ES cell of claim 29 is not taught by Thomson.

Accordingly, it is respectfully submitted that the rejection based on Thomson et al. under 35 U.S.C. §102(b) is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 1, 2, 3, 13-15 and 29 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Carpenter et al. (Pub. No. US2002/0019046 A1).

The Examiner contends that Carpenter et al. teach primate pluripotent stem cells, and specifically refer to the embryonic stem cells taught by Thomson. Thus, the Examiner contends that Carpenter et al. anticipate claims 1, 2, 13-15 and 29.

The rejection insofar it concerns claims 1-2 and 13 is rendered moot in view of the cancellation of these claims. Furthermore, claims 14-15 and 29, as presently amended, are directed to progenitor cells or undifferentiated ES cells which are produced culturing undifferentiated ES cells in the presence of noggin and characterized by a lack of at least one marker of the original undifferentiated ES cells prior to the culturing. Carpenter et al. do not teach culturing undifferentiated ES cells in the presence of noggin, or any cells resulting from such culture and characterized by a lack of at least one marker of the original undifferentiated ES cells. Therefore, Carpenter et al. do not teach the progenitor cells of claims 14-15 or 29.

With respect to claim 3, the Examiner contends that Carpenter et al. teach methods for directing the differentiation of ES cells into various specific somatic cell lineages. In particular, Carpenter et al. allegedly teach using the TGF-β antagonist, noggin, for generating neurons. Therefore, the Examiner concludes that claim 3, which simply requires providing ES cells and culturing such cells in the presence of noggin, is anticipated by Carpenter et al.

The rejection of claim 3 is rendered moot in view of the cancellation of claim 3. However, Applicants wish to address the rejection as if it had been applied to claim 25. Claim 25, as presently amended, is directed to a method of culturing undifferentiated ES cells in the presence of an indirect and direct antagonist of a BMP-mediated default pathway of extraembryonic endoderm differentiation, wherein the ES cells remain in an undifferentiated state after the culturing. Applicants submit that Carpenter et al. do not teach the method as presently claimed in claim 25, wherein the ES cells remain in an undifferentiated state after the culturing, e.g., an intermediate state where the undifferentiated ES cells lack at least one marker of original undifferentiated ES cells before the culturing, yet lack the features of differentiated cells (such as neuronal cells). Therefore, claim 25 would not be anticipated by Carpenter et al.

Accordingly, the rejection under 35 U.S.C. §102(e) based on Carpenter et al. is overcome. Withdrawal of the rejection is therefore respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

Frank S. DiGiglio
Registration No. 31,346

SCULLY, SCOTT, MURPHY & PRESSER
400 Garden City Plaza
Garden City, New York 11530
(516) 742-4343

XZ:ab
Enclosures:

- Certified copies of priority documents;
- New abstract;
- *Developmental Biology* 245, 83-94 (2002) (Exhibit 1)